DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 21 2005

Mr. Carlos T. Angulo
Zuckerman Spaeder LLP
1201 Connecticut Avenue, N.W.
Washington, D.C. 20036

Re: Docket No. 2002P-0493/CP1

Dear Mr. Angulo:

This responds to your citizen petition and supplement dated November 20, 2002, and June 12, 2003, respectively, on behalf of Andrx Pharmaceutical Corp. requesting that the Food and Drug Administration (FDA) deny approval of Proctor and Gamble/Astra Zeneca's (the sponsors') application to market Prilosec (omeprazole) over-the-counter (OTC) (hereafter referred to as Prilosec OTC).

In brief, your petition and supplement assert that the sponsors (1) did not meet their burden of showing that consumers could use Prilosec OTC safely and effectively in an OTC setting; (2) did not conduct sufficient clinical studies to assess the risks associated with OTC use of the product; and (3) did not develop adequate labeling to address these risks.

As you know, FDA approved Prilosec OTC on June 20, 2003. In conjunction with the approval, Charles Ganley, M.D., Director, Division of Over-the-Counter Drug Products, drafted a memorandum dated June 20, 2003 (Ganley Memorandum), addressing the points raised in your petition and supplement. While not a formal Agency response to the petition, the Ganley Memorandum represented the Agency's position on the petition and the approval of Prilosec OTC. The memorandum was posted on the Internet on June 20, 2003, and can be found at www.fda.gov/cder/drug/infopage/prilosecotc/default.htm. We have attached the Ganley Memorandum to this response.

The Ganley Memorandum articulated why we believe that the sponsors met their burden of showing that consumers can use Prilosec OTC safely and effectively in an OTC setting, citing two safety and efficacy studies, actual use and label comprehension studies, and significant differences in the labeling of Prilosec OTC compared to that of the prescription version. The memorandum also noted how the short-term use of Prilosec OTC and product labeling alleviated our concerns with regard to (1) masking symptoms of serious conditions and (2) preventing patient misuse. Finally, the memorandum stated that we had evaluated the name *Prilosec OTC* for potential consumer confusion (since it is for a different use than prescription Prilosec) and determined that the name Prilosec OTC was not misleading to consumers and would not result in unsafe use or medication errors. (See FDA's response dated January 21, 2005, to the citizen petition filed by Mattingly, Stanger & Malur, dated August 12, 2003, pages 6-7. Docket No. 2003P-0366/CP1.)

02P-0493

PDN1

Since we issued the Ganley Memorandum, we have not become aware of any information that would cause us to reconsider our position regarding your petition and supplement.

Therefore, we are reaffirming the positions stated in the attached Ganley Memorandum and denying your petition for the reasons set forth in the memorandum.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research

Attachments

**MEMORANDUM**

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
**Division of Over-the-Counter Drug Products (HFD-560)**

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Date: June 20, 2003

From: Charles J. Ganley, M.D.
Director, Division of Over-the-Counter Drug Products (HFD-560)

Subject: Andrx Citizen Petition regarding Prilosec OTC (NDA 21-229)

To: Jonca Bull, M.D.
Director, Office of Drug Evaluation V

Florence Houn, M.D.
Director, Office of Drug Evaluation III

We are aware of a Citizen Petition dated November 21, 2002, submitted on behalf of Andrx Pharmaceutical Corp., requesting that FDA deny the approval of the Proctor and Gamble's (the sponsor's) application to market Prilosec (omeprazole) over-the-counter (OTC).

The petition itself identifies three major points and then proceeds to identify a number of specific issues. These three points are addressed first followed by a response to the specific grounds articulated in the petition.

A supplement to their petition dated June 12, 2003 requests that the agency submit the studies completed since the meeting of the Joint Nonprescription & Gastrointestinal Drugs Advisory Committees (Joint Advisory Committee) on June 21, 2002 to another advisory committee session, in an open public forum, before approval action is taken. This point is listed as the fourth major point.

## I. The Petition's Major Points (Petition at 1)

1. The sponsor's NDA should be denied because they have not met their burden of showing that consumers can use Prilosec OTC safely and effectively in an OTC setting.

Based on FDA's review of the sponsor's application, we believe that they have met their burden of showing that consumers can use Prilosec OTC safely and effectively in an OTC setting. The sponsor submitted two adequately controlled studies to demonstrate efficacy and safety (Study 171 and 183) for a population of frequent heartburn sufferers.[1] The sponsor has also conducted five actual use studies and five label comprehension studies in order to assess the risks associated with OTC use of the product and establish how best to ensure its safe and effective use by consumers. In the most recent review cycle, the sponsor submitted Study 22103. This label comprehension study provided sufficient information to

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[1] Dr. Justice Division Director memo dated June 19, 2003

respond to the deficiencies described in the August 8, 2002 approvable letter.[2] FDA has reviewed these studies and concluded that the application should be approved because Prilosec OTC is safe and effective for its intended use.[3]

The petitioner has not provided any new data or new information to support their concerns. All of the issues raised by the petitioner were raised in FDA reviews of the sponsor's data or during FDA advisory committee meetings[4] to discuss the OTC availability of Prilosec, and have been satisfactorily resolved. The petitioner's interpretation of the data is inconsistent with the interpretation of the data of the majority of the experts at the June 21, 2002 Advisory Committee. At the conclusion of its proceedings, the Joint Advisory Committee voted 16 to 2 that pending modifications to the product labeling, confirmed by a label comprehension study, Prilosec OTC was safe and effective for OTC use. Based on the merits of the data, we concurred with the recommendations of the advisory committee and concluded that Prilosec OTC is safe and effective for OTC use.[5]

2. Even if OTC Prilosec could be used safely and effectively in an OTC setting, the sponsor has not conducted sufficient studies to assess the risks associated with OTC use of the product or to establish how best to ensure its safe and effective use by consumers.

As noted above, the sponsor has completed five actual use studies and five label comprehension studies in order to assess the risks associated with OTC use of the product and establish how best to ensure its safe and effective use by consumers. The development of drugs for OTC marketing is an iterative process often depending on multiple consumer behavior studies such as actual use and label comprehension studies. The petitioner suggests that an actual use study[6] is warranted to address remaining issues but has not described why the information needed must be obtained from an actual use study as opposed to a label comprehension study. The advisory committee identified the consumer behavior issues that required further study and recommended a labeling comprehension study as the mechanism to obtain the information.[7] We agreed with their recommendation. As discussed above, the final label comprehension study provided sufficient information to address our concerns described in the August 8, 2002 approvable letter and for us to conclude that Prilosec OTC is safe and effective for OTC use.[8]

3. Even if no additional studies are necessary, Prilosec OTC should not be approved until the sponsor makes significant changes to the product label, including but not limited to those changes recommended by the Joint Advisory Committee.

Significant changes have been made to the label, as summarized in my review dated June 20, 2003. The sponsor conducted a label comprehension study that evaluated consumer comprehension of the Use, Warnings and Directions sections of the label. Based on the review of this study,[9] we believe that the sponsor has provided adequate information to support the OTC marketing of Prilosec OTC.

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[2] Dr. Ganley Division Director memo dated June 20, 2003

[3] Dr. Chin review dated October 17, 2000; Dr. Lechter reviews dated May 23, 2002, and May 2, 2003; Dr. Shetty reviews dated October 25, 2000, May 10, 2002, and April 25, 2003

[4] October 20, 2000 and June 21, 2002.

[5] Dr. Ganley Division Director memo dated June 20, 2003.

[6] The petition has used the term "clinical Study" instead of "actual use Study", although "actual use Study" more accurately represents the requests made in the petition.

[7] June 21, 2002 Advisory Committee transcripts

[8] Dr. Ganley Division Director memo dated June 20, 2003

[9] Dr. Shetty April 23, 2003 review and Dr. Lechter May 2, 2003 review

4. The agency should submit the studies completed since the meeting of the Joint Nonprescription & Gastrointestinal Drugs Advisory Committees (Joint Advisory Committee) on June 21, 2002 to another advisory committee session, in an open public forum, before approval action is taken.

The question of whether to consult an advisory committee regarding issues involved in our review of human prescription drug products is committed solely to FDA's discretion as described in 21 CFR 14.171. We reviewed the single study submitted by the sponsor of the application since the June 21, 2002 advisory committee meeting and believe it is a well-conducted study. This study, in addition to the previous information submitted to the application, provides sufficient information to support the approval of Prilosec OTC. There are no remaining issues that warrant further discussion before an advisory committee. After deliberations were completed at the June 21, 2002 advisory committee meeting, the committee noted they did not need to reconsider the issues raised unless we felt there to be a need.[10]

## II. Specific Statement of Grounds

1. The petitioner asserts that while prescription Prilosec has been shown to be safe and effective for *symptomatic* heartburn associated with GERD, the sponsor have not demonstrated that consumers can use Prilosec OTC safely and effectively for the different purpose of *frequent* heartburn (Petition at 2). Additionally, the petitioner asserts that even if Prilosec OTC could be used safely and effectively by consumers in an OTC context for the prevention of heartburn, the sponsor have not demonstrated that conditions for safe and effective use are present. To do so, the petitioner maintains, the sponsor must (1) study the unsupervised use of the drug and identify the risks likely to result from such use, and (2) develop adequate labeling that will apprise consumers of these risks. The sponsor has done neither, the petitioners argue, "despite the abundant evidence that consumers will not use OTC Prilosec in the manner directed by the manufacturer and that such misuse can cause Prilosec 1 to be used in an unsafe and ineffective manner" (Petition at 2,3).

Heartburn is accepted by the agency to be a symptom that consumers can identify and self treat in the OTC setting.[11] In the past, the OTC indications for heartburn medicines have been limited to acute symptom relief and prevention of meal or beverage induced heartburn. The indication for Prilosec is a new indication for a population of frequent heartburn sufferers (occurring two or more days per week). The sponsor has conducted two efficacy/safety studies and numerous consumer behavior studies (actual use and label comprehension) to support the safety and efficacy of OTC omeprazole. The safety and effectiveness of OTC omeprazole has been scrutinized at two different FDA Advisory Committee meetings, and FDA has conducted numerous reviews of these studies. After reviewing the data in the most recent amendment to their NDA, we believe the sponsor has provided sufficient information to support the safe and effective OTC marketing of omeprazole for frequent heartburn.[12]

The petitioner has requested that the sponsor "study the unsupervised use of the drug and identify the risks likely to result from such use". The sponsor has done just that with Study 007[13], which was discussed by the Advisory Committee on June 21, 2002. This study was the primary study for the committee to review. Based on this study, the advisory committee voted overwhelmingly to support the approval of OTC Prilosec.[14] In the course of their deliberations, they recommended that additional testing be conducted to address some of the deficiencies in consumer behavior identified by Study 007. The

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[10] June 21, 2002 advisory committee transcripts at 318

[11] 21 CFR 331

[12] Dr. Ganley Division Director memo dated June 20, 2003.

[13] Dr. Shetty review dated April 16, 2002

[14] The committee voted 16 for and 2 against approval of the application. (June 21, 2002 Advisory committee transcripts at 231.)

committee recommended a label comprehension study, rather than an actual use study, to evaluate pending labeling issues. We agreed with their recommendation. The sponsor conducted Study 22103, which we have concluded supports the approval of the application.[15] By successfully conducting this study, the second part of the petitioner's request, "develop adequate labeling that will apprise consumers of these risks", has been achieved. Based on the results of Study 22103, we believe the sponsor has developed adequate labeling that will apprise the consumer of important risks.

2. The petitioner asserts that the sponsor has not demonstrated that consumers are able to self-select and de-select appropriately and that those who do self-select will use OTC Prilosec safely and effectively (e.g., following label use directions for duration of use and knowing when seek advice from a healthcare provider (Petition at 11).

The petitioner fails to note that the development of OTC drug products is an iterative process. Label comprehension and actual use studies often identify situations where consumers may not understand how to appropriately use the product. The sponsor has conducted five actual use and five label comprehension studies during the development of this product. Most of the concerns associated with the petitioner's statement are based on the outcomes of the earlier studies, which helped to identify the areas that required further study.

For the final phase in the development of this product, the sponsor conducted Study 22103. This was one of the largest label comprehension studies that we have asked a sponsor to conduct. It evaluated three different labels and assessed the comprehension in literate and low literate consumers with frequent or infrequent heartburn. We have accepted the results of this study as supportive of the final label.[16] As discussed above, this final study provided sufficient information to respond to all outstanding labeling deficiencies and for us to conclude that Prilosec OTC is safe and effective for OTC use.

3. The use of Prilosec 1 in an OTC setting creates the potential for masking serious diseases and for delays in the treatment of these diseases – the sponsor must conduct actual use studies to assess the extent of extended self-medication and potential masking problems (Petition at 13-16). The petitioner provides the following evidence:

   - Evidence presented before the Joint Advisory Committee indicated that (1) the effectiveness of Prilosec 1 for heartburn prevention increased over time, making it likely that consumers could continue to take the drug for recurrent heartburn after the end of the 14-day course of treatment to prevent heartburn; (2) consumers did not follow labeling instructions on how to take the drug and when to consult a physician; and (3) consumers in fact did not see a physician if their heartburn returned after 14 days – despite label warnings that recurring symptoms could be a sign of a serious condition.

   - Data presented to the Joint Advisory Committee revealed 49 cases of stomach cancer in patients taking Prilosec 1, four of which may have been masked by Prilosec 1 therapy. (Petition at 14).

During the development program, we had concerns regarding the masking of more serious conditions. The following points taken collectively address the resolution of this issue:

- During the June 21, 2002 advisory committee meeting, the committee voted on two questions relevant to this issue. First, with regard to the actual use Study 007, the committee was asked " Did consumers who had a reoccurrence of heartburn symptoms respond appropriately?" The committee voted 12 yes

[15] Dr. Ganley Division Director memo dated June 20, 2003

[16] Dr. Ganley Division Director memo dated June 20, 2003

and 6 no. Even though study subjects did not always follow the instructions on the label, the committee felt they often took appropriate alternative actions. Second, the committee was asked "...is the proposed 14 day duration of therapy acceptable for this population?" The committee voted 17 yes to 1 no. We have adopted a 14 day course of therapy as the recommended regimen.

- The short-term use of this product is not a concern in masking symptoms. The product is labeled appropriately to alert consumers about appropriate use. The serious conditions that are cause for concern include erosive esophagitis, Barrett's esophagus and esophageal cancer. Prilosec is an appropriate treatment for erosive esophagitis and Barrett's esophagus. Esophageal cancer is relatively rare and is the least likely to occur of the three. This issue was discussed extensively at the June 21, 2002 advisory committee and they did not believe it to be a major concern. We agree.

- This concern of masking more serious disease is not only applicable to this product but to other OTC heartburn products and other categories of OTC products. For these products, we believe this concern has been adequately addressed by labeling. For example, other acid reducers (e.g., H2 antagonists) are labeled for use for not more than 2 weeks, and internal analgesics (e.g. acetaminophen, nonsteroidal anti-inflammatory drugs) are labeled for use for not more than 10 days.

- The labeling and packaging for Prilosec OTC includes the following to encourage correct use[17]:
  - 14 tablet package configurations to encourage use for a 14-day course;
  - instructions that limit the repetitive use and the number of courses to be used per year;[18]
    (These instructions were added to the label as a result of the final label comprehension study.)
  - Warnings that alert consumers about other symptoms that may be a sign of a more serious condition.[19]
    (These were also added to the label as a result of the final label comprehension study.)

- Study 22103 evaluated the comprehension of the Use, Warning and Directions sections of a new label and found the comprehension to be high.[20]

4. The petitioner asserts that Prilosec OTC is ineffective for preventing heartburn at the initiation ("Day One") of treatment, creating the potential for unsafe and ineffective uses of the drug in an OTC setting. The petitioner maintains that the sponsor must conduct additional studies to examine the issue of interaction of Prilosec OTC with other acid reducers, develop labeling that communicates the risks of drug/drug interactions, and conduct studies on the reasons for overdosing (Petition at 16-20). Specifically, the petitioner states that:

   - Prilosec has not been proven effective in preventing heartburn during the first 24 hours and only achieves maximum effect after several days, potentially causing consumers to take other anti-heartburn medications at the same time, to an uncertain effect, or to take excessive doses.

   - Evidence suggests that misuse did occur during actual use trials (Petition at 17) while no studies have been conducted on the reasons, extent, and risks of overdosing (Petition at 20).

The petitioner has incorrectly stated the results of the efficacy data. The sponsor conducted Studies 171 and 183, which show that 20 mg of omeprazole showed a significant treatment effect during

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[17] Dr. Ganley Division Director memo dated June 20, 2003.

[18] "Directions" section of the final labeling

[19] "Do not use" and "Ask a doctor before use" if you have sections of the final labeling

[20] Dr. Shetty April 23, 2003 review and Dr. Lechter May 2, 2003 review

the first day.[21] Approximately 50% of the subjects receiving 20 mg omeprazole compared with approximately 30% of placebo subjects had no heartburn during the first day. So, in fact, some people get complete relief of symptoms on the first day. The percentage of persons experiencing complete relief in the omeprazole group continued to increase on subsequent days.

The sponsor did conduct an additional study and tested the concept that complete relief may not occur on the first day. In Study 22103 the sponsor tested whether consumers would understand that some might not achieve a full effect of the therapy on the first day. Approximately 91% of study participants tested on this concept understood it.[22] The labeling of the product reflects the results from this study. The sponsor has made changes to the labeling to reflect that it may take 1 - 4 days for a full effect to occur.[23]

The petitioner has raised questions about the concomitant use of other heartburn medications with Prilosec OTC. This may be particularly relevant when someone first initiates therapy with Prilosec and the maximum benefit has not been realized. We considered what should be said in the labeling and determined that the label should remain silent. This determination is based on the following information, which demonstrates that we do not have sufficient data at this point to support labeling limitations on the use of these drugs: (1) Current prescription labeling permits the concomitant use with antacids, and pharmacokinetic data, as noted by the petitioner, gives conflicting results about an interaction; and (2) There is little clinical information about the interaction of an H2 blocker and a proton pump inhibitor. In addition, if there were an interaction, it would most likely be decreased efficacy (we have no data to suggest a safety issue). The consequence of decreased efficacy is that the product would not provide a benefit and the consumer would not purchase it again. If symptoms recur and they follow labeled instructions, they would then seek the advice of a doctor. Finally, it is unreasonable to expect them to conduct additional studies because this issue is also applicable to other prescription proton pump inhibitors.

5. The petitioner asserts that drug/food interactions, which have generally been found to hinder the effectiveness of Prilosec, have not been sufficiently studied to permit use of the drug in an OTC setting (Petition at 21). The petitioner surmises that this will lead to misuse of the product.

The sponsor has conducted a food effect study. Based on the FDA review of this information[24], there does appear to be a food effect. The final labeling of Prilosec OTC addresses this by instructing consumers to take before eating in the morning. These instructions were similar to the instructions used in one of the clinical efficacy studies that support the indication.

The likelihood of misuse (e.g. taking more than the recommended amount) is more likely to occur in the prescription setting than in the OTC setting because of safeguards incorporated into packaging and labeling of the OTC product:

- The labeling states "do not take more than one tablet a day".
- The OTC product is packaged as 14-day courses of therapy. This is more likely to limit the excessive use of the OTC product compared to a prescription product that may be dispensed in amounts sufficient to supply 1 - 3 months of therapy.
- Study 22103 tested whether subjects knew when to take the product. Comprehension for this concept was close to 90%.[25] Even low literate subjects (≈ 80 - 85% comprehension ) did quite well in understanding this concept.

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[21] Dr. Justice Division Director memo dated June 19, 2003.

[22] From table 20 - 21 of Dr. Shetty's review dated April 23, 2003.

[23] The sponsor tested language stating "for some, it may take 1-2 days for full effect". In the efficacy studies, the increase in response appears to plateau at day 4. The final labeling reflects this finding.

[24] Biopharm Review Dr. Al-Fayoumi dated November 13, 2000

[25] From table 20 - 21 of Dr. Shetty's review dated April 23, 2003

6. The petitioner states that the sponsor have not adequately explained the risks associated with the use of contraindicated medications other than anti-heartburn medications in conjunction with Prilosec 1, nor have they adequately justified their decision as to as to which drug/drug interactions to note on the OTC Prilosec label. The petitioner asserts that the sponsor must (1) conduct studies evaluating the drug-drug interactions associated with OTC Prilosec, comparing the relative severity of these interactions with one another; and (2) provide FDA with a clear and compelling reason for the inclusion or exclusion of any particular contraindicated medicine on the product label (Petition at 22-25). Specifically, the petitioner:

   - States that while the proposed label for OTC Prilosec alerts consumers that they should see a physician before using the drug if they are taking warfarin, phenytonin, or ketoconaxole, the proposed label is likely to be ineffective in steering people away from OTC Prilosec when taking these drugs (Petition at 23-24).

   - Asserts that even if the labeling on contraindicated medicines were adequate with respect to warfarin, phenytonin, or ketoconazole, the sponsor failed to list other drugs, suggested in prescription Prilosec, that interact in a clinically significant manner with omeprazole (e.g., drugs needed for the proper absorption of gastric acid).

The OTC labeling rule[26] requires that information on drug interactions be incorporated into the **Ask a doctor or pharmacist before use if you are** section of the labeling. Because this information will be in the same location on all labels, this will allow consumers to locate and identify drugs with relative contraindications for use with the product. There are many currently marketed OTC drug products that include possible drug-interactions. As the Drug Facts labels become widely available, we expect comprehension of potential interactions with other drugs to improve. The petitioner cites the results from a label comprehension study that suggests frequent heartburn sufferers using medications listed on the label self selected correctly 50% of the time.[27] It is important to note that this improved to 82 % when a list of brand names was given. This result is consistent with the results of a labeling comprehension study suggesting > 80% comprehension on scenarios related to concomitant use of medications.[28] In lieu of including numerous brand names in the Drug Facts labeling, (we would never be able to include them all), we required a brief descriptor on the label for each drug listed. We did not believe additional testing was needed for this concept.

The final Prilosec label lists warfarin, antifungal medicines, diazepam and digoxin in the **Ask a doctor or pharmacist before use if you are** section of the Drug Facts label. We met with the sponsor on January 30, 2001 and decided that these drugs should be included on the label based on possible risks to the consumer.[29] At that time clarithromycin was also considered for the list but later discounted because it causes elevations in omeprazole levels and does not impact on clarithromycin levels. We did not believe that elevated levels of omeprazole related to this interaction with clarithromycin was of significant clinical concern. Although the interaction with digoxin and warfarin is minimal, we decided to include them because of the narrow therapeutic index for both drugs.

7. The petitioner states that the sponsor have not adequately evaluated the risks associated with the use of Prilosec OTC by certain sub-populations (such as those of Asian origin), and have not developed product labeling to warn these sub-populations of these risks (Petition at 25)

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[26] 21 CFR 201.66

[27] June 21, 2002 advisory committee transcripts at 147

[28] June 3, 1998 review of Dr. Lechter and Dr. Aiken (include in Dr. Lechter review of August 16, 2000). Original Study 1

[29] Meeting minutes of January 30, 2001 meeting between FDA and Proctor and Gamble

The petitioner has not provided any data to suggest that sub-populations such as Asians experienced increased incidence of adverse events despite the marketing of the product for 14 years in the prescription setting. The hypothesis surmised in the FDA review[30] cited by the petitioner is hypothetical and the possible consequences are more likely to occur in the prescription setting. They refer to comments by Dr. Michael Wolf at the advisory committee who surmises that long term use can lead to increased gastrin and *potentially* (emphasis added) to more serious diseases long term. Any concerns about the long-term use of this product in various sub-populations are more applicable to the prescription use of the product where patients remain on therapy for extended periods of time.

The petitioner suggests that this sponsor be required to conduct studies to further evaluate the long-term effects of omeprazole in these sub-populations. We disagree. This product is recommended for short-term use (14-day course), and based on the data the sponsor has provided, we believe the majority of consumers will follow the labeled instructions and understand the possible risk of misuse.

We do not believe warnings on the label for these sub-populations are necessary because

- the product is limited to a 14-day treatment period,
- there is no data from the prescription safety database to suggest that these populations experience excess risk.
- in the event some sub-populations may accumulate omeprazole in the blood, there is no evidence that this is harmful over a short period of time.

8. The petitioner states that even if the sponsor's application is approved, Prilosec 1 should be renamed to avoid consumer confusion since it is for a different use than prescription Prilosec (Petition at 26)

The name "Prilosec 1" was withdrawn by the sponsor and replaced with the proposed name "Prilosec OTC". The Division of Medical Errors and Technical Support conducted a review of the proposed name "Prilosec OTC" to determine the potential for confusion with approved proprietary and established names as well as pending names and concluded that there are no objections to the use of the proprietary name, Prilosec OTC. [31]

[30] Dr. Mark Avigan review dated January 27, 2000
[31] Division of Medical Errors and Technical Support consult by- D. Toyer 10-11-02

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

Charles Ganley
6/20/03 05:08:28 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

JAN 21 2005

Food and Drug Administration
Rockville MD 20857

John R. Mattingly
Mattingly, Stanger & Malur
1800 Diagonal Road
Suite 370
Alexandria, VA 22314

Docket No. 2003P-0366/CP1

Dear Mr. Mattingly:

This letter responds to your citizen petition dated August 12, 2003 (Petition), requesting that the Food and Drug Administration (FDA) amend its approval of Prilosec OTC to require that it be sold under a different brand name to reduce consumer confusion and decrease the potential for misuse of the product.

We have carefully considered your petition as well as comments to the petition submitted by Mylan Pharmaceuticals (Mylan) dated September 12, 2003, December 11, 2003, February 2, 2004, and October 29, 2004; and by Procter & Gamble dated September 26, 2003 (by Covington & Burling), March 29, 2004, and November 19, 2004.

For the reasons discussed below, your petition is denied.

## I. BACKGROUND

On June 23, 2003, FDA approved Prilosec OTC (omeprazole magnesium), 20 milligrams (mg),[1] for the treatment of frequent heartburn occurring 2 or more days a week. Omeprazole capsules (10, 20, and 40 mg) remain available by prescription (under the trade name Prilosec) for the treatment of gastroesophagael reflux disease (GERD), including the treatment of heartburn.

## II. DISCUSSION

### A. Patient Misuse

You assert that the Agency did not address the issue of patient misuse in its June 20, 2003, memorandum on Andrx Pharmaceutical Corporation's (Andrx's) citizen petition (Docket No. 02P-0493/CP1) requesting that FDA deny approval of Prilosec OTC.[2]

[1] Prilosec OTC contains 20.6 mg of omeprazole magnesium equivalent to 20 mg of omeprazole.

[2] In conjunction with our approval of Prilosec OTC, Charles Ganley, M.D., Director, Division of Over-the Counter Drug Products, drafted a memorandum, dated June 20, 2003 ("Ganley Memorandum"), which addresses the points raised in Andrx's petition (a copy of the Ganley Memorandum is attached hereto). While not a formal Agency response to the petition, it represented the Agency's position on the petition and approval. The memorandum can be found at www.fda.gov/cder/drug/infopage/prilosecotc/default.htm. Concurrently with the issuance of this response to your petition, we are issuing a response to the Andrx petition that reaffirms the positions stated in the Ganley Memorandum.

Specifically, you claim that prescription (Rx) Prilosec and Prilosec OTC are sold under the same name and cause consumer confusion in that Prilosec and Prilosec OTC carry different indications (Petition at 3).

We disagree. The Ganley Memorandum addresses potential patient misuse through FDA's review of the sponsors' extensive label comprehension and actual use studies (Ganley Memorandum at 2 to 6). As the Ganley Memorandum concludes, the reviewed studies demonstrate a high level of consumer understanding regarding (i) directions for use of the OTC product and (ii) the conditions under which a patient should seek medical attention. In addition, the Ganley Memorandum specifically addresses risks associated with unsupervised use of Prilosec OTC and how the approved labeling and packaging for Prilosec OTC encourages its proper use. As explained in the Ganley Memorandum, we do not believe there will be significant patient misuse of Prilosec OTC.

**B. Use of the *Prilosec* Name in the OTC Product**

You assert that the marketing of the OTC omeprazole product as Prilosec OTC carries the connotation that it is the same product (at the same strengths and for the same intended use) as prescription *Prilosec*. (Petition at 3). You state that this may mislead consumers to inappropriately self-diagnose and self-treat conditions, such as GERD, that should otherwise be diagnosed and monitored by a licensed medical professional. (Petition at 4). Finally, you add that the misuse and misunderstanding of Prilosec OTC may result in increases in disease-state morbidity and health care costs (Petition at 3).

We disagree with your assertions for the following reasons. First, as stated in the Ganley Memorandum, the sponsors conducted label comprehension and actual use studies that evaluated consumer comprehension of the *Uses*, *Warnings*, and *Directions* sections of the label. These studies were designed to identify potential situations where consumers may not understand how to appropriately use the product. The sponsors completed five actual use and five label comprehension studies during the course of development of Prilosec OTC to assess the risks associated with the product.

Study 22103 specifically tested label comprehension for labels containing the Prilosec OTC trade name. This large study (1,842 subjects) showed high levels of comprehension regarding directions for use and when to seek medical attention. Specifically, more than 93% of test subjects understood the labeled warnings about *other conditions or serious conditions*; more than 95% understood the proper dosage and the duration of therapy; and more than 93% understood what to do if repeat episodes occurred.

Second, Prilosec OTC is packaged in unit-of-use configurations as a 14-day course of therapy. This was designed to limit the chronic use of the OTC product and ensure better compliance with the recommended limitations of therapy. In comparison, the prescription product is usually dispensed in bulk for 1 to 3 months of therapy.

Third, you do not provide any data or case reports to substantiate your claims of patient confusion and potential adverse events due to use of the Prilosec OTC name. Nevertheless, we conducted a search and analysis of our postmarketing adverse event database to identify potential concerns of inappropriate use that might warrant revision of the product labeling (i.e., the name of the product) as you urge. We have concluded, however, that although there may be some evidence of very limited patient use of the OTC product for Rx-labeled indications, such reports represent a miniscule fraction of the number of units of Prilosec and Prilosec OTC sold and do not appear to represent a significant phenomenon. Thus, there is insufficient cause to require a labeling change at this time.

From June 2003 (when Prilosec OTC was approved) to February 2004, the Agency received 124 domestic adverse event reports for all omeprazole products, including Rx, OTC, and generic omeprazole. In that same period, approximately 196 million capsules of prescription Prilosec and nearly 95 million tablets of Prilosec OTC were sold in the United States.[3]

The majority of the adverse event reports either specifically described the use of Rx Prilosec or did not provide enough product information to determine whether the OTC or Rx product was used. Twelve of 124 reports (9.7%), however, specified the use of Prilosec OTC for the following indications that are not labeled for the OTC product: GERD (6), gastritis (2), ulcer (2), and Barrett's esophagus (2). In 3 of the 12 cases (25%), consumers used twice the recommended dose (40 mg/day). In 2 of the 12 cases (17%), Prilosec OTC was used beyond the labeled 14 days of therapy. And in 6 of the 12 cases, the reported adverse events were likely related to the use of the product itself, and not misuse due to confusion with the Rx product. Those adverse events included allergic reactions (2), abdominal pain/itching (1), and lack of efficacy (3). None of these six cases reported hospitalization as an outcome, and only one case reported that a medical intervention was required. The remaining six instances of adverse events were most likely related to an underlying medical condition or a concomitant medication.

To summarize, there is evidence of only very limited patient use of the OTC product for Rx-labeled indications, and these reports represent a very small fraction of the number of units of Prilosec and Prilosec OTC sold. Thus, there is insufficient cause to require a labeling change at this time. Nevertheless, the Agency will continue to monitor trends that might indicate increasing instances of misuse of Prilosec OTC.

[3] IMS Health, IMS National Sales Perspective, 2001-2003 (data extracted March 2004). For OTC products, the Retail & Provider Perspective captures 36 percent of dollar volume of total sales. IMS then projects that figure to a national number to account for retail outlets that might not otherwise be captured, such as airports and newsstands. IMS did not begin to capture Prilosec OTC sales data until September 2003.

### C. Impact of Advertising Campaign

You assert that the "massive" direct-to-consumer (DTC) advertising campaign for prescription Prilosec has resulted in widespread consumer association of the Prilosec name with the prescription product and its indications. You claim that this recognition of the Prilosec name will cause consumers to believe that the uses of Prilosec OTC are the same as those of Prilosec (Petition at 3-4). You further state that Prilosec OTC signifies the first Rx-to-OTC transition since 1997 in which a new therapeutic class of OTC ingredients has been approved for limited strengths and indications compared to the coexisting prescription product. You contend that this is notable because DTC advertising was not widely used at the time of previous similar Rx- to-OTC switches but has proliferated since 1997. You therefore assert that the dangers of consumer bias and confusion based upon brand name recognition resulting from DTC advertising did not exist when products such as Tagamet and Zantac entered the OTC market (Petition at 5-6).

We do not agree that DTC advertising of Prilosec will cause confusion between Prilosec and Prilosec OTC. According to information we received from the sponsors, DTC advertising for Prilosec ceased in December 2001. The OTC product was launched in September 2003. Given this 22-month gap, consumer confusion with regard to the OTC product does not appear to be likely, and you have failed to address this significant gap in your petition, or to provide any support for your claim that DTC advertising can condition consumers "forever."

You claim that the "purple pill" advertisements for prescription Prilosec for the treatment of GERD have conditioned consumers to associate "purple pill" with treatment of GERD. You assert that this is likely to lead consumers to the inappropriate use of Prilosec OTC to self-treat conditions such as GERD that instead should be evaluated, diagnosed, and treated by a physician. You add that this may result in a worsening of the consumer's condition, or the development of other serious gastrointestinal diseases such as erosive esophagitis and its potential sequalae, esophageal cancer (Petition at 4).

Your "purple pill" argument fails because Prilosec OTC is a *pink* tablet and is not being advertised as the "purple pill." Consumers therefore are likely to experience little, if any, confusion based on the product's appearance, or on the description of prescription Prilosec as a "purple pill."

Finally, you state that advertisements describing prescription Nexium as the "new purple pill," with an indication for GERD add to potential consumer confusion regarding intended uses between the Prilosec OTC and Nexium (Petition at 4, 5).

We disagree. While Nexium is being advertised as the "new purple pill," its brand name has no similarity to the name Prilosec OTC. Therefore, we do not believe that the Nexium campaign is likely to cause consumer confusion.

### D. Look Alike, Sound Alike

You note that in 1990, Prilosec's name was changed, at FDA's request, from Losec, which was being confused with the diuretic Lasix (furosemide). You contend that using the same brand name in both the prescription and OTC omeprazole products further elevates the risk of medication error because the names for both products not only look alike and sound alike, they literally are the same (Petition at 6).

We disagree that use of the name Prilosec OTC increases the risk of medication error. Like Prilosec OTC, a number of OTC products have the same active moiety and product name as their prescription counterpart with only a modifier, such as OTC, in their name -- even though they have different indications. Examples of these products include Motrin IB, Zantac75, Pepcid AC, and Tagamet HB. Moreover, as discussed in section II.B of this response, there is insufficient evidence of patient confusion or incidence of adverse events to warrant a name change for the Prilosec OTC product. Similarly, we are unaware of significant adverse events associated with the above-mentioned OTC drugs that might demonstrate that product misuse is occurring due to consumer confusion with their prescription counterparts.

Your reference to the 1990 name change from Losec to Prilosec is misplaced because Lasix (the drug with which there was potential confusion) was a drug with different active moieties and different indications. Any potential confusion between Prilosec and Prilosec OTC could not lead to the type of medication error involving two different active moieties or even drug classes.

### E. Response to Mylan Comments

Mylan Laboratories, Inc. submitted comments in support of the petition in which it made several claims concerning alleged patient confusion and misuse of Prilosec OTC, some of which were raised long after the petition was filed. Although the Petitioner did not seek some of the relief or make some of the arguments that Mylan raised in its comments, we respond for the sake of comprehensiveness.

Mylan states that FDA did not weigh the risk of abuse of Prilosec OTC for treating more severe conditions such as those indicated for Rx Prilosec, potentially endangering consumers because the interchangeability of Prilosec and Prilosec OTC is being assumed "by all segments of our health care sector" (Mylan December 11, 2003, comment at 1).

Mylan did not describe specific risks due to "assumed interchangeability of Prilosec and Prilosec OTC" or provide any adverse event data associated with such a substitution. Nevertheless, as discussed in section II.B above, we analyzed our postmarketing database to identify potential concerns of inappropriate use and concluded that there is insufficient evidence of patient confusion or incidence of adverse events to warrant a name change for the Prilosec OTC product. The risk of long-term abuse of Prilosec OTC was extensively considered by the Agency and is discussed in the Ganley Memorandum at 2-6.

Mylan asserts that Prilosec OTC is neither bioequivalent nor therapeutically equivalent to prescription Prilosec (Mylan December 11, 2003, comment at 1, 2). Because Prilosec OTC was approved on the basis of separate efficacy and safety data in its new drug application (NDA) submitted in accordance with section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(1)), Prilosec OTC was not required to be bioequivalent or therapeutically equivalent to Prilosec to be approved. The legal construct of § 505(j) is completely irrelevant to whether Prilosec and Prilosec OTC can bear similar proprietary names.

Mylan suggests that because Prilosec and Prilosec OTC have different active ingredients they must have different names (Mylan October 29, 2004, comment at 1, 2). Mylan states that a name is improper under FDA's regulations if "similarity in spelling or pronunciation may be confused with the proprietary name or established name of a different drug or ingredient" (Mylan October 29, 2004, comment at 1, citing 21 CFR 201.10(c)(5), 202.1(a)(5)).

Mylan erroneously contends that FDA's regulations "cannot possibly be interpreted as allowing . . . different active ingredients . . . to be sold under the *same* trade name." (Id. at 2)(emphasis in original). These arguments, as explained below, are incorrect. Under FDA regulations, different active ingredients may be sold under similar trade names unless consumers "may be confused" by use of the similar name. This is evident in 21 CFR 201.10(c)(5), which provides that "[t]he labeling of a drug *may be* misleading" (emphasis added) because the proprietary name of "a drug or ingredient . . . *may be* confused with the proprietary name . . . of a different drug or ingredient" (emphasis added). 21 CFR 202.1(a)(5) provides that advertising cannot designate a drug or ingredient by proprietary name "that *may be* confused with the proprietary name . . . of a different drug or ingredient")(emphasis added).

As discussed extensively in the Ganley Memorandum, there is evidence that consumers are not confused by the use of the Prilosec OTC name. The studies show that consumers know that the drug provided over-the-counter differs from the prescription Prilosec product, are aware of the different indications for the products, and understand the directions and duration for taking the OTC product before seeking medical attention.

These actual use studies demonstrate that people use the drugs correctly and in appropriate circumstances, and are not misled into thinking that by taking "Prilosec OTC" they are in fact taking Prilosec.

Finally, in determining whether or not a product's name is misleading under Section 502(a) of the Act, the agency considers whether any potential confusion regarding active ingredients (such as described in the regulations, 21 CFR 201.10(a)(5) and 202.1(a)(5)) may lead consumers to believe that products with different effects will have the same effects. These regulations are intended to address situations not found here, where similar proprietary names could cause consumers to mistakenly use a drug that would not have the desired therapeutic effect. Prilosec and Prilosec OTC refer to products that contain the same active moiety, omeprazole, which is solely responsible for the products' identical pharmacological effect. Patients therefore are not at risk of being confused as to the pharmacological effect of the two products.

FDA's approach here is not new. For example, based on similar reasoning, FDA approved the use of the name "Advil" in OTC products that contain the same active moiety but different active ingredients (ibuprofen both with free acid and with potassium salt).

Mylan cites AstraZeneca's August 2003 submission to the U.S. Patent and Trademark Office requesting a patent term extension on various patents describing prescription Prilosec and Prilosec OTC as containing different active ingredients. As with Advil, that OTC versions of the same active moiety contain different active ingredients does not control whether omeprazole and a different salt can both contain "Prilosec" in their trade names.

Mylan contends that consumers are at risk because of health insurer/formulary activity following the launch of Prilosec OTC, specifically due to health plans "directing patients to take the OTC Prilosec product in place of current prescription products on which patients are maintained" (Mylan September 12, 2003, comment at 1, 2). The Agency does not regulate medical practice or the policies of health insurers and/or formulary decision makers. As discussed extensively in this response and the attached Ganley Memorandum, we believe that Prilosec OTC is adequately labeled for all segments of the health care sector.

## III. CONCLUSION

For the reasons stated above, we deny your request to require that Prilosec OTC be sold under a different brand name. Our analysis of the suitability of the Prilosec OTC brand name was consistent with our analysis of previous naming requests, including instances where a modifier was added to a brand name for OTC marketing. We analyzed our postmarketing database to identify potential concerns of inappropriate use and/or patient

confusion with regard to Prilosec OTC and prescription Prilosec and concluded that there is insufficient evidence of patient confusion or incidence of adverse events to warrant a name change for the Prilosec OTC product. Therefore, your petition is denied.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research

Attachment